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        Richard Dennis DiMarchi
        David Lee Smiley
        Lianshan Zhang
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       MODIFIED GLUCAGON-LIKE PEPTIDE-1 ANALOGS
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<220>
       Synthetic construct
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<221>
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<222>
       (32)..(32)
<223>
       Xaa = Ser, Pro, or His
```

1

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       (33)..(33)
       Xaa = Ser, Arg, Thr, Trp, or Lys
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<223>
       Xaa = Ser or Gly
<220>
<221>
<222>
       MISC_FEATURE
        (35)..(35)
<223>
       Xaa = Ala, Asp, Arg, Glu, Lys, or Gly
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<221>
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<222>
        (36)..(36)
       Xaa = Pro, Ala, L-Cys, D-Cys, homocysteine, penicillamine, NH2 or
<223>
<220>
       MISC_FEATURE
<221>
<222>
        (37)..(37)
       Xaa = Pro, Ala, L-Cys, D-Cys, homocysteine, penicillamine, NH2 or
<223>
        is absent
<220>
<221>
        MISC_FEATURE
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        (38)..(38)
       Xaa´ = Pro´, Ala, Arg, Lys, His, NH2, L-Cys, D-Cys, homocysteine, penicillamine, NH2, or is absent
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        (39)..(39)
        Xaa = Ser, His, Pro, Lys, Arg, Gly, L-Cys, D-Cys, homocysteine, penicillamine, NH2, or is absent
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        (40)..(40)
       Xaa = His, Ser, Arg, Lys, Pro, Gly, L-Cys, D-Cys, homocysteine, penicillamine, NH2, or is absent
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        MISC_FEATURE
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        (41)..(41)
       Xaa = His, Ser, Arg, Lys, L-Cys, D-Cys, homocysteine, penicillamine, NH2, or is absent
<223>
<220>
<221>
<222>
        MISC_FEATURE
        (42)..(42)
<223>
        Xaa = Gly, His, L-Cys, D-Cys, homocysteine, penicillamine, HN2,
        or is absent
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        (43)..(43)
        Xaa = Pro, His, L-Cys, D-Cys, homocysteine, penicillamine, NH2 or
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        is absent
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       MISC_FEATURE
<221>
<222>
        (44)..(44)
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x15642.NatlPhase.ST25.txt
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penicillamine, NH2, or is absent
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       (45)..(45)
      Xaa = L-Cys, D-Cys, homocysteine, penicillamine, NH2, or is
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       absent
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Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Gly Pro Xaa 20 25 30
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<211>
       31
<212>
       PRT
<213>
      Artificial
<220>
<223>
       Synthetic construct
<220>
<221>
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       Xaa = L-histidine, D-histidine, desamino-histidine,
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       2-amino-histidine beta-hydroxy-
       histidine, homohistidine, alpha-fluoromethyl-histidine, or
       alpha-methyl-histidine
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       (2)..(2)
       Xaa = Ala, Gly, Val, Leu, Ile, Ser, or Thr
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       (6)..(6)
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       Xaa - Phe, Trp, or Tyr
<220>
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       (10)..(10)
       Xaa = Val, Trp, Ile, Leu, Phe, or Tyr
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       (12)..(12)
<223>
       Xaa = Ser, Trp, Tyr, Phe, Lys, Ile, Leu, Val
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<221>
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       (13)..(13)
<223>
       Xaa = Tyr, Trp, or Phe
<220>
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<223> Xaa = Leu, Phe, Tyr, or Trp
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       Xaa = Gly, Glu, Asp, Lys
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       Xaa = Ala, Val, Ile, or Leu
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       (21)..(21)
       Xaa = Glu, Ile, or Ala
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<223> Xaa = Ala or Glu
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       Xaa = Val or Ile
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Xaa Xaa Glu Gly Thr Xaa Thr Ser Asp Xaa Ser Xaa Xaa Xaa Glu Xaa
                                      10
Gln Ala Xaa Lys Xaa Phe Ile Xaa Trp Leu Xaa Lys Gly Arg Lys
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<212>
       PRT
<213> Artificial
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<223> Synthetic construct
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<221>
       MISC_FEATURE
<222>
        (1)..(1)
       Xaa = L-histidine, D-histidine, desamino-histidine,
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       2-amino-histidine, beta-hydroxy-
       histidine, homohistidine, alpha-fluoromethyl-histidine, or
       alpha-methyl-histidine
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       xaa = Gly, Ala, Val, Leu, Ile, Ser, or Thr
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<222>
        (10)..(10)
       xaa = Val, Phe, Tyr, or Trp
<223>
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į,

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       (12)..(12)
       Xaa = Ser, Tyr, Trp, Phe, Lys, Ile, Leu, or Val
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       (16)..(16)
       Xaa = Gly, Glu, Asp, or Lys
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       (19)..(19)
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       Xaa = Ala, Val, Ile, or Leu
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<223>
       Xaa = Val or Ile
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                                      10
Gln Ala Xaa Lys Glu Phe Ile Ala Trp Leu Xaa Lys Gly Arg Lys
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       Synthetic construct
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<223>
       2-amino-histidine, beta-hydroxy-
       histidine, homohistidine, alpha-fluoromethyl-histidine, or
       alpha-methyl-histidine
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       (2)..(2)
<223>
       Xaa = Ala, Gly, Val, Leu, Ile, Ser, or Thr
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Xaa = Phe, Trp, or Tyr
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       (10)..(10)
       Xaa = Val, Trp, Ile, Leu, Phe, or Tyr
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<222>
       (12)..(12)
       Xaa = Ser, Trp, Tyr, Phe, Lys, Ile, Leu, Val
<223>
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       (14)..(14)
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       Xaa = Leu, Phe, Tyr, or Trp
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       Xaa = Gly, Glu, Asp, or Lys
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Xaa = Ala, Val, Ile, or Leu
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Xaa = Gly, Pro, or Arg
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       (31)..(31)
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       Xaa = Gly, Pro, Ser, or Lys
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<221>
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<223>
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       MISC_FEATURE
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       Xaa = Ser, Arg, Thr, Trp, Lys, NH2 or is absent
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        MISC_FEATURE
<222>
        (34)..(34)
       Xaa = Ser, Gly, Lys, NH2 or is absent
<223>
<220>
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f

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       xaa = Pro, Ala, Lys, NH2 or is absent
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       xaa = Pro, Ala, Lys, NH2 or is absent
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       (38)..(38)
       Xaa = Pro, Ala, Arg, Lys, His, NH2 or is absent
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       Xaa = Ser, His, Pro, Lys, Arg, NH2 or is absent
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       Xaa = His, Ser, Arg, Lys, NH2, or is absent
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       (41)..(41)
       xaa = His, Ser, Arg, Lys, NH2, or is absent
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       (42)..(42)
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Gln Ala Xaa Lys Xaa Phe Ile Xaa Trp Leu Xaa Xaa Gly Xaa Xaa Xaa 20 25 30
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
         35
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       11
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      Artificial
<213>
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       Synthetic construct
<220>
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        (1)..(1)
       Xaa = L-histidine, D-histidine, desamino-histidine,
2-amino-histidine, beta-hydroxy-
<223>
```



histidine, homohistidine, alpha-fluoromethyl-histidine, or alpha-methyl-histidine

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       (2)..(2)
       Xaa = Gly, Val, Leu, Ile, Ser, or Thr
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       Xaa = Val, Trp, Ile, Leu, Phe, or Tyr
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       Xaa = Gly, Glu, Asp, or Lys
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       (19)..(19)
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       Xaa = Ala, Val, Ile, or Leu
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       (27)..(27)
Xaa = Val or Ile
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       MISC_FEATURE
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       (28)..(28)
<223>
       Xaa = Lys, Asp, Arg, or Glu
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       (30)..(30)
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       Xaa = Gly, Pro, or Arg
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       (31)..(31)
       Xaa = Gly, Pro, Ser or Lys
<223>
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       MISC_FEATURE
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       (32)..(32)
       Xaa = Ser, Pro, His, Lys, NH2 or is absent
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       (33)..(33)
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       Xaa = Ser, Arg, Thr, Trp, Lys, NH2 or is absent
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       Xaa = Ser, Gly, Lys, NH2 or is absent
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       Xaa = Ala, Asp, Arg, Glu, Lys, Gly, NH2 or is absent
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<220>
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<222>
       (36)..(36)
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x15642.NatlPhase.ST25.txt
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       (37)..(37)
       xaa = Pro, Ala, Lys, NH2, or is absent
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       xaa = Pro, Ala, Arg, Lys, His, NH2 or is absent
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       (39)..(39)
       xaa = Ser, His, Pro, Lys, Arg, NH2 or is absent
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       Xaa = His, Ser, Arg, Lys, NH2 or is absent
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<222>
        (41)..(41)
       Xaa = His, Ser, Arg, Lys, NH2 or is absent
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        (42)..(42)
       xaa = Lys, NH2, or is absent
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                                        10
Gln Ala Xaa Lys Glu Phe Ile Ala Trp Leu Xaa Xaa Gly Xaa Xaa Xaa
<210>
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       Synthetic construct
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        (1)..(1)
        Xaa = L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, beta-hydroxy-histidine, homohistidine, alpha-fluoromethyl-histidine, or alpha-methyl-histidine
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       Xaa = Gly, Val, Leu, Ile, Ser, or Thr
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       (16)..(16)
      Xaa = Gly, Glu, Asp, or Lys
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      (19)..(19)
      Xaa = Ala, Val, Ile, or Leu
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       (27)..(27)
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      Xaa = Val or Ile
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       (32)..(32)
<223> Xaa= Ser, Pro, His, Lys, NH2 or is absent
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       (33)..(33)
       Xaa = Ser, Arg, Thr, Trp, Lys, NH2 or is absent
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       (34)..(34)
       xaa = Ser, Gly, Lys, NH2 or is absent
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       Xaa = Ala, Asp, Arg, Glu, Lys, Gly, NH2 or is absent
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       Xaa = Pro, Ala, Lys, NH2 or is absent
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      Xaa = Pro, Ala, Lys, NH2 or is absent
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       (38)..(38)
       Xaa = Pro, Ala, Arg, Lys, His, NH2 or is absent
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       (39)..(39)
       Xaa = Ser, His, Pro, Lys, Arg, NH2 or is absent
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       Xaa = His, Ser, Arg, Lys, NH2, or is absent
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       (41)..(41)
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x15642.NatlPhase.ST25.txt
       Xaa = Lys, NH2, or is absent
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Gln Ala Xaa Lys Glu Phe Ile Ala Trp Leu Xaa Lys Gly Gly Pro Xaa 20 25 30
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        Synthetic construct
       MISC_FEATURE
       Xaa = L-histidine, D-histidine, desamino-histidine,
       2-amino-histidine, beta-hydroxy-histidine, homohistidine, alpha-fluoromethyl-histidine, or alpha-methyl-histidine
       MISC_FEATURE
       Xaa = Ala, Gly, Val, Leu, Ile, Ser, or Thr
       MISC_FEATURE
       Xaa = Phe, Trp or Tyr
       MISC_FEATURE
        Xaa = Val, Trp, Ile, Leu, Phe, or Tyr
        MISC_FEATURE
       Xaa = Ser, Trp, Tyr, Phe, Lys, Ile, Leu, Val
       MISC_FEATURE
       Xaa = Tyr, Trp, or Phe
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Xaa = Leu, Phe, Tyr, or Trp <223>

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(42)..(42)

<223>

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13

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PRT

Artificial

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(6)..(6)

(10)..(10)

(12)..(12)

(13)..(13)

MISC_FEATURE

(14)..(14)

<223> Xaa = Gly, Glu, Asp, or Lys

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Xaa = Ala, Val, Ile, or Leu
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Xaa = Gly, Pro, or Ser
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       Xaa = Ser, Pro, or His
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Xaa = Pro, Ala, Lys, NH2 or is absent
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X15642.NatlPhase.ST25.txt
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      Xaa = Ser, His, Pro, Lys, Arg, NH2 or is absent
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      xaa = His, Ser, Arg, Lys, NH2 or is absent
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      MISC_FEATURE
<222>
      (41)..(41)
      xaa = His, Ser, Arg, Lys, NH2, or is absent
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       (42)..(42)
      Xaa = Lys, NH2, or is absent
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       (45)..(45)
      Xaa = Lys, NH2 or is absent
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Gln Ala Xaa Lys Xaa Phe Ile Xaa Trp Leu Xaa Xaa Gly Xaa Xaa Xaa 20 25 30
40
<210>
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      Xaa = Ser, Arg, Thr, Trp, or Lys
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<223>
      Xaa = Ser, or Gly
<220>
      MISC_FEATURE
<221>
<222>
       (35)..(35)
      Xaa = Ala, Asp, Arg, Glu, Lys, or Gly
<223>
<220>
      MISC_FEATURE
<221>
<222>
       (36)..(36)
      Xaa = Pro, Ala, Lys, NH2 or is absent
<223>
<220>
<221>
<222>
       MISC_FEATURE
       (37)..(37)
<223>
       Xaa = Pro, Ala, Lys, NH2 or is absent
<220>
<221>
       MISC_FEATURE
<222>
       (38)..(38)
       Xaa = Pro, Ala, Arg, Lys, His, NH2 or is absent
<223>
<220>
<221>
       MISC_FEATURE
<222>
       (39)..(39)
<223>
       Xaa = Ser, His, Pro, Lys, Arg, NH2 or is absent
<220>
<221>
       MISC_FEATURE
<222>
       (40)..(40)
<223>
       Xaa = His, Ser, Arg, Lys, NH2 or is absent
<220>
<221>
<222>
      MISC_FEATURE
       (41)..(41)
      Xaa = His, Ser, Arg, Lys, NH2 or is absent
<223>
<220>
<221>
<222>
       MISC_FEATURE
       (42)..(42)
       Xaa = Lys, NH2, or is absent
<223>
<220>
<221>
       MISC_FEATURE
<222>
       (43)..(43)
<223>
       Xaa = Pro, His, Lys, NH2 or is absent
<220>
<221>
       MISC_FEATURE
<222>
       (44)..(44)
       Xaa = Ser, His, Lys, NH2 or is absent
<223>
<220>
<221>
       MISC_FEATURE
<222>
       (45)..(45)
       Xaa = Lys, NH2 or is absent
<223>
<400> 14
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x15642.NatlPhase.ST25.txt
His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
                                     10
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Gly Pro Xaa 20 25 30
<210>
       15
       31
<211>
<212>
       PRT
       Artificial
<213>
<220>
<223>
       Synthetic construct
<220>
<221>
       MISC_FEATURE
<222>
       (1)..(1)
       Xaa = L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, beta-hydroxy-
<223>
       histidine, homohistidine, alpha-fluoromethyl-histidine, or
       alpha-methyl-histidine
<220>
       MISC_FEATURE
<221>
<222>
       (2)..(2)
       Xaa = Ala, Gly, Val, Leu, Ile, Ser orThr
<220>
<221>
       MISC_FEATURE
<222>
       (6)..(6)
<223>
       Xaa = Phe, Trp, Tyr
<220>
<221>
<222>
       MISC_FEATURE
       (10)...(10)
       xaa = Val, Trp, Ile, Leu, Phe, or Tyr
<223>
<220>
<221>
       MISC_FEATURE
<222>
       (12)..(12)
       Xaa = Ser, Trp, Tyr, Phe, Lys, Ile, Leu, Val
<220>
<221>
       MISC_FEATURE
<222>
       (13)..(13)
       Xaa = Tyr, Trp, or Phe
<223>
<220>
       MISC_FEATURE
<221>
<222>
       (14)..(14)
       Xaa = Leu, Phe, Tyr, or Trp
<223>
<220>
<221>
       MISC_FEATURE
<222>
       (16)..(16)
<223>
       Xaa = Gly, Glu, Asp, Lys
<220>
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<221>

MISC_FEATURE

```
x15642.NatlPhase.ST25.txt
```

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<222> (19)..(19)
<223> Xaa = Ala, Val, Ile, or Leu
<220>
       MISC_FEATURE
<221>
<222> (21)..(21)
<223> Xaa = Glu, Ile, or Ala
<220>
<221> MISC_FEATURE
<222> (24)..(24)
<223> Xaa = Ala or Glu
<220>
<221> MISC_FEATURE
<222> (27)..(27)
<223> Xaa = Val or Ile
<220> '
<221> MISC_FEATURE
<222>
       (31)..(31)
       Xaa = Gly, His, Lys, or NH2 or is absent
<223>
<400> 15
Xaa Xaa Glu Gly Thr Xaa Thr Ser Asp Xaa Ser Xaa Xaa Xaa Glu Xaa
Gln Ala Xaa Lys Xaa Phe Ile Xaa Trp Leu Xaa Lys Gly Arg Xaa
                                 25
<210> 16
<211> 31
<212> PRT
<213> Artificial
<220>
<223> Synthetic construct
<400> 16
His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly 25 30
<210>
       17
<211> 39
<212> PRT
<213> Artificial
<220>
<223> Synthetic construct
<400> 17
His Val Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Ile Lys Gly Gly Pro Ser 20 25 30
```

```
Ser Gly Ala Pro Pro Pro Cys
35

<210> 18
<211> 39
<212> PRT
<213> Artificial
```

<220> <223> Synthetic construct

<220>
<221> MOD_RES
<222> (39)..(39)

<400> 18

His Val Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu $1 \ \ \,$ 10 $\ \ \,$ 15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Ile Lys Gly Gly Pro Ser 20 25 30

Ser Gly Ala Pro Pro Pro Cys 35

<210> 19 <211> 32 <212> PRT <213> Artificial

<220> <223> Synthetic construct

<400> 19

His Val Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu 1 5 10 15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Ile Lys Gly Arg Gly Cys 20 25 30

<210> 20 <211> 32 <212> PRT <213> Artificial <220> <223> Synthetic construct

<220>
<221> MOD_RES
<222> (32)..(32)
<223> S-sulfonate (SSO3) is attached to the thiol of Cys at position 32

<400> 20

His Val Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu 1 5 10 15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Ile Lys Gly Arg Gly Cys 20 25 30

<210>

<211> 32 <212> PRT

Artificial <213>

<220>

<223> Synthetic construct

<400> 21

His Val Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu 1 5 10

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Ile Lys Gly Arg Gly Lys 20 25 30

<210> <211>

<210> 22 <211> 32 <212> PRT

Artificial <213>

<220>

Synthetic construct

<220>

<221> MOD_RES

<222>

(32)..(32)
[3-(2-pyridyldithio)propanamide]amide is attached to Lys at <223> position 32

<400> 22

His Val Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu 1 5 10 15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Ile Lys Gly Arg Gly Lys 20 25 30

<210> 23

<211> 39

<212> PRT

<213> Heloderma suspectum

<220>

<221> MISC_FEATURE

<222> (1)...(39)

<223> Exendin-3

<400> 23

His Ser Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Page 29

1

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser $20 \hspace{1cm} 25 \hspace{1cm} 30$

Ser Gly Ala Pro Pro Pro Ser 35

5

24 39 <210>

<211> <212>

PRT

Heloderma suspectum

<220>

<221> MISC_FEATURE

<222> (1)..(39)

<223> Exendin-4

<400>

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu $1 \ \ \,$ 15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser 20 25 30

Ser Gly Ala Pro Pro Pro Ser 35